Division of Diabetes, Endocrinology and Metabolic Diseases

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September 2001 Council

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1001 RACE/ETHNIC DISPARITIES IN THE INCIDENCE OF DIABETES COMPLICATIONS (PAS-00-028)

http://grants.nih.gov/grants/guide/pa-files/PAS-00-028.html

FY 2002 Action

This Program Announcement (PA) was issued in 2000 and is active through 2003. The PA solicits research to investigate: (1) differences among contemporary racial and ethnic minority populations in the U.S. in risk factors for complications of diabetes and in rates of these complications; and (2) the extent to which factors, including inherent metabolic and genetic variations, medical care, socioeconomic status, and behavior account for these differences.

Background

Information on the incidence of diabetic complications in the U.S. is often based on community populations or large clinic populations in which the onset of diabetes occurred several decades ago. These studies generally found a striking excess of microvascular disease in minority groups, including Native Americans, African Americans and Hispanic Americans. Whether these disparities in diabetes complications continue to occur in contemporary diabetic patients is not known.

Some of the racial differences in diabetic complications may be explained by differences in availability and quality of health services. Differences in self-care practices, health care provider practices, and/or access to quality health care and prevention services may directly impinge on the frequency and magnitude of risk factors for diabetes complications and the intensity of medical care for early stages of complications to prevent progression to end-stage disease.

Differences in blood glucose, lipid and blood pressure control may be modified by improved medical care. In addition, genetic susceptibility and other biological risk factors may contribute in unknown ways that lead to complications. This is suggested by clustering of complications (especially nephropathy) within families and by the excess risk of retinopathy in Hispanics versus non-Hispanics that remains when the degree of hyperglycemia exposure is taken into account.

Finally, lifestyle, psychosocial factors, stress, family structure, social support, diet and culture, and socioeconomic status vary among racial and ethnic minorities and may contribute to differential risk of developing diabetes complications and progression of complications. Little is known about how these behavioral factors influence the risk of complications and the effectiveness of interventions designed to prevent or reduce complications on racial and ethnic minority groups.

Identification of these divergent etiologies and quantification of their correlation to risk have important implications for prevention and amelioration of microvascular complications. Such information might improve the effectiveness of treatment to reduce the disparities in the incidence of diabetes complications among racial and ethnic groups.

In contrast to microvascular complications, racial and ethnic minorities with diabetes often have lower rates of macrovascular disease than Caucasian population groups. The factors that account for the differing macrovascular disease rates are unknown.

Research Goals and Scope

The overall objectives of this PA are to determine: (1) whether contemporary racial or ethnic minority populations continue to differ in their risk for microvascular and macrovascular complications; and, if so, (2) the reasons for these differences. It is recognized that both biologic and non-biologic factors may be operating in these populations.

Approaches may include metabolic, genetic and/or epidemiologic studies in representative populations. Advantage might be taken of extant cohort studies that may have been established for investigation of diabetes or other diseases. Alternatively, investigators may propose to start a new cohort, appropriately powered, to capture the current risks and outcomes in an era of improved medications for glycemic, blood pressure and lipid control.

Investigators are encouraged to incorporate appropriate surrogate markers for complications into study design to shorten the duration of studies. Such surrogate markers might include early indicators of end-stage complications (background retinopathy, albuminuria, serum creatinine, basement membrane thickening, EKG, carotid ultrasound).

Appropriate topics for investigation would include but are not limited to:
(1) epidemiologic studies to determine the rates of diabetic complications in appropriate representative samples of contemporary populations; (2) studies to identify genes which might affect the development of complications in different populations; (3) state-of-the-art, hypothesis-driven metabolic studies to determine whether there are differences in metabolism, insulin sensitivity, energy expenditure, beta cell function, and body composition that might influence glycemic control and risk of complications in different populations; and (4) studies to investigate factors, such as medical care, behavior and lifestyle, and socioeconomic status, that may contribute to risk for development and progression of complications. Understanding the basis for differing susceptibilities could provide information that would lead to specific therapies likely to be useful in various subpopulations at high risk for the development of diabetes complications.

1002 RACIAL AND ETHNIC DIFFERENCES IN THE ETIOLOGY OF TYPE 2 DIABETES IN MINORITY POPULATIONS (PAS-99-166)

http://grants.nih.gov/grants/guide/pa-files/PAS-99-166.html

FY 2002 Action

This Program Announcement solicits research to expand understanding of the underlying metabolic, genetic, epidemiologic, sociocultural, and behavioral mechanisms that contribute to the racial and ethnic differences in the etiology of type 2 diabetes in the U.S.

Background

It is well recognized that there are major differences in the prevalence of type 2 diabetes among race-ethnic groups in the U.S. Substantial progress has been made toward identifying population-based risk factors for the development of type 2 diabetes that might lead to these race-ethnic disparities. Such established risk factors include, for example, genetic predisposition, total and central obesity, duration of obesity, high caloric intake, and physical inactivity. Factors such as socioeconomic status, acculturation and stress may also be important. Although these diabetes risk factors appear to operate in all race-ethnic groups, it is not known whether specific groups are inherently different in the ways they respond to risk factors, which may lead to their differential susceptibility to diabetes. Environmental, genetic and metabolic differences may underlie the disparity in diabetes rates, and physiological outcomes of risk factors may arise from a complex interplay of genetic and nongenetic (behavioral, lifestyle, and environmental) factors. Epidemiologic studies have documented the differing risk for diabetes among race-ethnic groups and have established the identity of diabetes risk factors. However, with few exceptions, these studies have not been designed to examine in depth the metabolic and physiologic effects of diabetes risk factors in specific race-ethnic populations. Consequently, there is an important need for carefully designed clinical studies to investigate these issues in representative samples of the various U.S. race-ethnic groups.

Research Goals and Scope

The overall objective of this PA is to determine, through studies in representative U.S. populations, the reasons for disparities in the incidence of type 2 diabetes in minority race-ethnic populations. Additionally, information that could emerge from these studies would be important for devising cost-effective approaches to phenotyping patients with type 2 diabetes and individuals at risk for this disease. The ability to characterize and identify discrete subgroups of type 2 diabetes patients would be essential in genetic studies of this disease. Appropriate topics for investigation might include state-of-the-art, hypothesis-driven metabolic studies in representative samples of U.S. race-ethnic groups; the temporal relationship of changes in body weight and body composition, glucose tolerance, and insulin resistance; beta cell function studies, such as beta cell assessments with longitudinal follow up, beta cell responses to fatty acids, hyperglycemia, arginine, and insulin resistance; clinical studies of fat metabolism and insulin resistance; temporal relationships among the components of Syndrome X; and investigations of the behavioral, socioeconomic, psychosocial, cultural, family, and community factors that influence the individual's risk for developing type 2 diabetes.

1003 ROLE OF ENDOTHELIAL DYSFUNCTION IN DIABETIC COMPLICATIONS (PA-00-026)
http://grants.nih.gov/grants/guide/pa-files/PA-00-026.html

FY 2002 Action
This Program Announcement was issued in 2000 and is active through 2003. Endothelial function is known to be abnormal in diabetes and may be an early step in the development of atherosclerotic lesions. Recent work has also focused attention on the role of endothelial function in the pathogenesis of microvascular complications. This PA is intended to stimulate the application of new molecular technologies to this area. Understanding the pathogenesis of endothelial dysfunction in diabetes at the molecular and cellular level will provide new targets for pharmacologic or genetic manipulations to prevent complications of diabetes.

Background
Diabetes is the leading cause of end-stage renal disease, blindness in adults, and non-traumatic lower leg amputations. In addition, individuals with diabetes have a two- to four-fold increased risk of developing, and dying from, cardiovascular disease. One in ten health care dollars in the U.S. is spent on diabetes; most of these health care costs are incurred in the treatment of macro- and microvascular complications.

Endothelial dysfunction is a key feature of diabetes and is thought to be a major cause of the associated vascular complications. Hyperglycemia itself appears to affect multiple mechanisms that increase atherosclerosis. Hyperglycemia enhances oxidation, thrombosis, inflammation, matrix production, and the formation of advanced glycation end products and other metabolites that can potentially damage the vasculature. Insulin may also play an important role in atherogenesis. Even in the absence of diabetes, patients with insulin resistance are at significantly increased risk for atherosclerosis. Insulin resistance is associated with hypertriglyceridemia and a preponderance of small, dense low-density lipoprotein (LDL). This LDL phenotype may be more susceptible to oxidative modification, a process that promotes atherosclerosis by impairing endothelial cell function, stimulating inflammation and adhesion, and promoting vascular smooth muscle cell changes. Insulin itself stimulates vascular smooth muscle cell migration, growth and matrix production, and enhances clot formation. Insulin resistance is also associated with impaired nitric oxide production.

Endothelial dysfunction may also contribute substantially to the pathogenesis of microvascular complications. Diabetic nephropathy results from changes in blood flow in small vessels with an increase in mesangial cells and excess accumulation of extracellular matrix. The earliest retinal abnormalities induced by hyperglycemia are impaired autoregulation of retinal blood flow and decreased retinal blood flow associated with loss of endothelial-supporting pericytes from retinal capillaries. These changes are followed by endothelial cell permeability changes and retinal capillary occlusion. In diabetic peripheral sensory neuropathy, capillary closure is frequently observed in the vasa nervorum, and endoneurial blood flow and oxygen tension are reduced.

The molecular basis of endothelial cell dysfunction in diabetes is not well understood. Hyperglycemia can cause increased free radical generation and oxidative stress, which has been implicated in endothelial cell dysfunction.

Determining the effects of hyperglycemia on endothelial function, and the subsequent role of endothelial abnormalities in the development of diabetic vascular lesions, is critical to understanding the etiology and pathogenesis of the micro- and macrovascular complications of diabetes. Dissecting these pathways will provide new targets for effective therapeutic or prevention strategies.

Research Goals and Scope

Recent advances in understanding endothelial cell biology; coupled with new molecular technologies, provide powerful tools for studying endothelial function in diabetes. In addition, there is clearly a need for the development of good animal models of diabetic complications, as well as of surrogate markers for monitoring the development and progression of complications. The use of such markers would also facilitate the study of potential pharmacologic agents that could be developed, based on a better understanding of the etiology and pathogenesis of diabetic complications. Appropriate topics for investigation in response to this PA would include: (1) studies to determine how hyperglycemia alters endothelial and/or vascular smooth muscle cell function, including changes in gene expression; (2) studies to determine what genes modulate susceptibility of tissues to hyperglycemia-induced injury; (3) studies to understand the sequence of events in the pathogenesis of hyperglycemia-induced vascular injury; (4) studies to determine how vascular inflammation is altered in diabetes; (5) studies to determine the effects of insulin in vascular cells at the molecular and physiologic levels; (6) studies to determine how specific alterations in circulating lipids in patients with diabetes affect the development and expansion of atherosclerotic lesions; (7) studies to determine how hyperglycemia or hyperinsulinemia alter hemostasis and cellular interactions at the surface of unstable atherosclerotic plaques; and (8) studies to evaluate how antidiabetic drugs affect the vasculature and the coagulation system, and determine what impact they may have on atherosclerosis development and progression.

1004 DEVELOPMENT OF THE ENDOCRINE PANCREAS (PAS-00-015)

http://grants.nih.gov/grants/guide/pa-files/PAS-00-015.html

FY 2002 Action

This program announcement is intended to stimulate the application of advances in developmental biology, specifically in developmental genetics, embryology and stem cell biology, to study pancreatic development. Collaborative efforts that link expertise in basic developmental biology or stem cell biology and diabetes are strongly encouraged. It is anticipated that this research will ultimately lead to a better understanding of the pathways required for the development and regeneration of the endocrine pancreas, both *in vivo* and *in vitro*. This PA, with set-asides of funds in FY 2000-2002, is intended to intensify investigator-initiated research, to attract new investigators to the field, and to encourage interdisciplinary approaches to research in this area.

Background

Type 1 and type 2 diabetes result from the anatomical and functional loss of insulin-producing beta cells of the pancreas. Replacement of these cells through regeneration or transplantation could offer lifelong treatment for diabetics. However, a major problem in implementing treatment is the lack of sufficient islet cell tissue for transplantation, and a lack of understanding of whether and how beta cells regenerate. Embryonic stem cells and other tissue-specific stem cells could potentially provide a limitless source of islet cells for transplantation therapies. Despite major advances in stem cell research and in defining specific developmental pathways in neurobiology and hematopoiesis, a fundamental understanding of the developmental pathways leading to formation of differentiated cells in the endocrine pancreas is still in its infancy.

Research Goals and Scope

Appropriate topics for investigation under this PA would include: (1) developmental genetic screens for identifying mutations in endoderm that affect pancreas development; (2) the identification of signals, signaling pathway components, and transcription factors that regulate endoderm specification, dorsal pancreatic bud formation, and pancreatic cell fate determination; (3) the role of cell-cell interactions, differential cell adhesion and cell motility in morphogenesis of the pancreas; (4) the role of extracellular matrix in islet cell morphogenesis; (5) molecular markers for defining all stages of pancreas development, including cell-specific markers of stem/progenitor cells of the endocrine pancreas; (6) studies examining endocrine pancreatic cell lineage, including alpha, beta, and delta cell fate determination and differentiation; (7) studies exploring the potential use of embryonic stem cells, hematopoietic, neural and other stem cells in the formation of differentiated cells of the endocrine pancreas; (8) identification of growth conditions required to generate differentiated cells of the endocrine pancreas from stem/progenitor cells; and (9) generating or using model systems for the study of regeneration of the endocrine pancreas.

1005 THE ROLE OF GROWTH FACTORS IN THE DEVELOPMENT OF DIABETES COMPLICATIONS (PA-99-159)
http://grants.nih.gov/grants/guide/pa-files/PA-99-159.html

FY 2002 Action
This Program Announcement was issued in 1999 and is active through 2002. While several growth factors are already being tested in clinical trials for the treatment and/or prevention of diabetic microvascular disease, a systemic examination of the pathophysiologic role of growth factors in diabetic complications is lacking. An understanding of the tissue and cell specific expression of growth factors in affected organs, and of the molecular action of these growth factors in the pathophysiology of complications will lead to improved, more specific therapies.

Background
Diabetic complications are a major public health concern. Diabetic retinopathy is the predominant cause of blindness in adults and diabetic nephropathy is a leading cause of end-stage renal disease. Diabetes is the most common reason for non-traumatic lower extremity amputations; over 50 percent of patients with diabetes experience some degree of neuropathy. Accelerated cardiovascular disease remains the major cause of mortality in patients with diabetes.

The pathologic findings seen in diabetic complications implicate growth factors in their development. Endothelial proliferation in the eye results in abnormal neovascularization of the retina. Accumulation of mesangial matrix is the hallmark of diabetic nephropathy. Atherosclerotic lesions involve accumulation of extracellular matrix, as well as proliferation of smooth muscle cells.

Studies strongly suggest a role for vascular endothelial growth factor (VEGF) in the pathogenesis of diabetic retinopathy; however, its exact mechanism of action is not understood. Studies are needed to understand the cascade of events triggered by VEGF and how hyperglycemia leads to VEGF up-regulation.

In the kidney, transforming growth factor (TGF)-beta appears to contribute to the basement membrane thickening characteristic of diabetic nephropathy. Levels of other growth factors, including insulin-like growth factor 1 (IGF-1), fibroblast growth factor (FGF), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF), are also altered; however, the role of these other growth factors in the pathogenesis of diabetic retinopathy and nephropathy is less well characterized than for VEGF and TGF-beta. Altered cytokine (e.g., tumor necrosis factor) expression may also contribute to endothelial dysfunction in diabetes.

Growth factor deficiency, rather than up-regulation, is thought to play a role in the pathogenesis of diabetic neuropathy. Levels of nerve growth factor (NGF) and IGF-1 are reduced in animals and humans with diabetic neuropathy; however, no direct connection has been made between reduced levels of neurotrophic factors and the development of diabetic neuropathy. In addition, there are multiple members of the nerve growth factor family, each of which is specifically trophic for a different neuronal population. Studies are needed to examine not only tissue-specific but also cell-specific expression of growth factors.

Despite much suggestive evidence implicating growth factors in the development of the complications of diabetes, much remains to be determined about their role in the pathophysiology of these disorders. Little is known about how multiple growth factors might interact with each other in a specific tissue; nor is it known how growth factors interface with other abnormalities that have been implicated in the etiology of complications, including altered metabolism of polyols, accumulation of advanced glycation end products, activation of protein kinase C or increased reactive oxygen species.

Finally, the study of diabetic complications is limited by the inability to sample tissues and by the long time that it takes for complications to develop. There is clearly a need for the development of good animal models of diabetic complications, as well as of surrogate markers for monitoring the development and progression of complications. The use of such markers would also facilitate the study of potential pharmacologic agents that could be developed based on a better understanding of the etiology and pathogenesis of these complications.

Research Goals and Scope

New technologies, including the use of genetic knockouts, transgenic animals and chip array technology, provide powerful tools for studying the expression of growth factors during the development of diabetic complications, and for determining the molecular basis for their actions. Appropriate topics for investigation under this PA would include, but are not limited to: (1) studies to evaluate the tissue and/or cell specific expression of growth factors during the development of complications, including a temporal analysis; (2) studies to determine what genes are up- or down-regulated by altered growth factor expression; (3) studies to determine whether growth factor signaling pathways are altered in diabetic complications; (4) studies to determine how hyperglycemia alters growth factor expression or action; (5) studies to determine how metabolic changes associated with complications interact with alterations in growth factor expression and/or action; and (6) studies to test the role of growth factors in the pathogenesis of diabetic complications using animal models (including the use of knockout or transgenic animals).

1006 INSULIN SIGNALING AND RECEPTOR CROSS-TALK (PAS-99-112)

http://grants.nih.gov/grants/guide/pa-files/PAS-99-112.html

FY 2002 Action

The purpose of this initiative is to stimulate novel and innovative research to investigate the fundamental underlying mechanism(s) of action of signaling through the insulin receptor and its cross-talk with other cellular receptors. Of particular interest is how such signaling interactions may affect the development and/or progression of diabetes and its complications. This announcement was initially issued in FY 1999 and is active through FY 2002.

Background

Diabetes mellitus is characterized by inappropriate regulation of serum glucose levels. Both type 1 and type 2 diabetes are characterized by insulin deficiency, with type 2 diabetes also characterized by cellular resistance to insulin action. Insulin acts through a cell surface receptor and several downstream effectors to regulate cellular growth and metabolism. Insulin target tissues also respond to hormones, growth factors and cytokines that signal through numerous other cell surface receptors, with potential effects on insulin-dependent cellular processes. Often a cellular response represents the net response to a number of signals (cross-talk). Some of the effects of insulin receptor action can occur relatively rapidly while others may require longer-term events and include changes in gene expression. Many of the actions of insulin and its receptor, such as effects on glucose transporters, have long been under study with several ongoing efforts having produced important and major advances, but with gaps in our understanding of the underlying mechanisms of action remaining to be filled. How the integration of cell signaling in insulin-dependent tissues occurs represents an important area of investigation with implications for the pathophysiology and therapeutics of diabetes.

Research Goals and Scope

The specific objectives of this research solicitation include, but are not limited to: (1) determination of the specificity of signaling through the insulin receptor, including delineation of metabolic versus mitogenic responses; (2) elucidation of the precise mechanism of action of the insulin receptor in mediating glucose uptake in insulin-sensitive tissues; (3) signaling through growth factor, cytokine or other cell surface receptors in insulin target tissues and potential role(s) in the pathophysiology of diabetes and its complications; (4) identification of novel factors associated with cell surface receptor action in insulin target tissues which may be involved in development of diabetes and its progression, and as putative targets for therapeutic intervention; (5) structural biology of cell surface receptors involved in diabetes and its complications; (6) delineation of pathways of signaling through the insulin receptor leading to specific transcription factor(s): role(s) in the development, progression, and treatment of diabetes; (7) interactions between and among transcription factors that mediate the effects of insulin on gene expression: cross-talk with transcription factors responding to other signaling pathways; (8) signaling cross-talk between the insulin receptor and other classes of cell surface or nuclear receptors and effects on regulation of the development and/or progression of diabetes and its complications; (9) factors which regulate expression on the cell surface of functional insulin receptors, and other cell surface receptors, in diabetes and its complications; (10) identification of factors involved in cell

signaling which may cause resistance to insulin action in target insulin-sensitive cells (e.g. muscle, adipose) and novel approaches to overcoming or bypassing such resistance; and (11) the mechanism of action of nonpeptide receptor analogs and their potential efficacy as therapeutic agents.

1007 TYPE 1 DIABETES TRIALNET (TRIALNET)
(RFA DK-01-003 and RFA DK-01-004)
http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-003.html
http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-004.html

FY 2002 Action
Two companion RFAs solicit clinical centers to perform intervention studies to preserve pancreatic beta cell function and prevent type 1 diabetes, and a coordinating center to provide clinical center coordination, analytical and statistical support for the clinical trials, and laboratory support. Investigators will complete the ongoing oral insulin study of the Diabetes Prevention Trial for Type 1 Diabetes (DPT-1) and participate in the design and execution of pilot and expanded studies of new agents to prevent or ameliorate type 1 diabetes, and in natural history and genetics studies in populations screened for or enrolled in these studies.

Background
This initiative responds to recommendations of the Diabetes Research Working Group (DRWG) that identified additional clinical trials of immunoprevention of type 1 diabetes (e.g., using antigen-specific, cytokine- or antibody-based immunotherapy) as an extraordinary research opportunity. The DRWG also recommended the establishment of a national diabetes trial network of cooperative clinical research groups to create a stable, high-quality infrastructure for the conduct of effective and efficient clinical trials in diabetes.

This initiative will also allow for completion of the DPT-1, an ongoing clinical trial to determine whether use of oral insulin in non-diabetic relatives of persons with type 1 diabetes can delay the development of diabetes. Oral insulin can delay the onset of type 1 diabetes in the non-obese diabetic mouse, perhaps serving as an immune modulator or toleragen. The parenteral insulin trial of the DPT-1 was completed in late spring 2001, with the finding that its use did not impact on development of diabetes compared to those only being closely monitored. The parenteral insulin trial had been initiated on the basis that it had been observed to prevent diabetes in animal models of spontaneous diabetes, could preserve beta cell function in newly diagnosed diabetic humans, and had delayed the development of type 1 diabetes in small pilot studies in prediabetic humans.

In the DPT-1, relatives of type 1 diabetic individuals are screened for islet cell antibodies of the pancreas, and if they are positive, they are staged to determine their risk for diabetes, based on further genetic, autoimmune, and metabolic factors. Those considered to be at intermediate risk for diabetes are eligible for randomization to either oral insulin (daily capsule of human insulin crystals) or placebo. Those who had been found to be at high risk for diabetes had been eligible for the parenteral insulin trial.

Recruitment is approximately 68 percent complete for the oral insulin trial. Participants are to be followed for at least two years. DPT-1 was originally funded through August 2001, and supported nine clinical centers and their associated networks of recruitment/retention sites participating in the DPT-1. Core support facilities included the operations coordinating center, data monitoring unit, laboratories, compounding and distribution pharmacies, and clinical cost reimbursement system.

To plan for future TrialNet studies in the prevention of type 1 diabetes, the NIDDK and DPT-1 investigators have convened meetings to discuss potential cohorts and agents, eligibility criteria, and outcome measures. Examples of potential cohorts include new onset type 1 diabetic subjects identified through the DPT-1 and individuals who have other markers of diabetes but who are ineligible for DPT-1. Examples of potential agents include antigen-based therapies such as recombinant human GAD65 and the heat shock protein hsp60 p277 peptide, monoclonal antibodies such as anti-CD3 and anti-CD25, and certain cytokine-based therapies. Multiple pilot studies could simultaneously test promising agents, and on the basis of these, expanded intervention studies might be launched.

The established DPT-1 network was thought to be an excellent platform on which to build an enhanced network that would comprise the TrialNet. Expansion of the number of recruitment sites would enhance recruitment of subjects for the DPT-1 and for future TrialNet studies. The DPT-1 population and populations identified by the TrialNet may be fruitful groups to study predisposing genes to type 1 diabetes and diabetic complications. Samples and associated data from participants of TrialNet may be entered into genetic repositories for use by investigators inside or outside the TrialNet.

Research Goals and Scope

Awards are being issued to expand the number of clinical centers to complete the DPT-1 and begin simultaneous pilot, feasibility and efficacy studies of new agents to preserve pancreatic beta cell function, as well as natural history and genetics studies. TrialNet will collaborate with the laboratories of the Immune Tolerance Network. The newly constituted Steering Committee will develop a mechanism to solicit, evaluate, and select new proposals for pilot and intervention and expanded studies that are submitted to the TrialNet.

1008 PREVENTION AND TREATMENT OF TYPE 2 DIABETES IN CHILDREN AND ADOLESCENTS--CLINICAL CENTERS AND COORDINATING CENTER (RFA DK-01-010 and RFA DK-01-011)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-010.html
http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-011.html

FY 2002 Action

Two cooperative agreement RFAs have been issued to develop clinical trials for the prevention and treatment of type 2 diabetes in children. RFA DK-01-010 solicited applications from potential study sites and RFA DK-01-011 solicited applications for a coordinating center to provide clinical center coordination, and analytical and statistical support for the clinical trials. Funding of the clinical centers and planning for the trials is expected to start in FY 2002.

Background

Type 2 diabetes is characterized by insulin resistance and impaired insulin secretion, although its precise etiology and pathogenesis are only incompletely understood. The public health impact of type 2 diabetes is enormous.

Clearly associated with aging and obesity, type 2 diabetes has traditionally been considered a disease of adults. Children are assumed to have type 1 diabetes, an autoimmune disease. However, recent epidemiologic data reveal an increasing number of cases of type 2 diabetes in the pediatric population, especially among adolescents and in certain minority populations. In general, population-based screening data are not available. Data culled from diabetes clinics in several locations suggest that the percentage of children diagnosed with diabetes who are classified as having type 2 diabetes has risen from less than 5 percent (prior to 1994) to 30 to 50 percent (after 1994). The increase in type 2 diabetes in children is presumed to be a consequence of widespread obesity and decreased physical activity.

Data from NHANES III suggest that up to one-third of adults who have type 2 diabetes may go undiagnosed. A similar situation may exist with children. In fact, the diagnosis of type 2 diabetes in children is often made because of routine laboratory screening being conducted as part of a school physical and not because the child presents to a health care provider with specific complaints. Thus, many children who do not receive such screening may go undiagnosed until they become symptomatic, at which time they may have been hyperglycemic for many years and are at high risk of developing diabetic micro- and macrovascular complications. In addition, significant numbers of children may not have frank diabetes, but may be at high risk of developing diabetes based on the presence of insulin resistance, impaired fasting glucose or impaired glucose tolerance. It is, therefore, imperative to establish appropriate screening criteria and effective primary prevention programs to avoid a potential major public health burden.

The majority of children with type 2 diabetes are in the pre-adolescent or adolescent age range. The adolescent period presents special challenges to health care providers and families when attempting to promote behavior and life style changes. Prevention and treatment programs must also consider cultural differences among racial and ethnic groups that may influence acceptance of medical regimens. This is especially important for type 2 diabetes in children, which disproportionately affects minority groups.

When children do develop diabetes, efficacious therapy is needed to maintain euglycemia in order to prevent the development of complications. Diabetes is currently estimated to cost the U.S. health care system approximately $98 billion annually. Much of the cost is related to the micro- and macrovascular complications of diabetes. Since the development of complications is related, in part, to the duration of diabetes, children represent a population at high risk. Unfortunately, the drugs currently approved for use in adults with type 2 diabetes have not been systematically studied in children. Thus, treatment options for those children diagnosed with type 2 diabetes are restricted by the lack of data on the use of such pharmacological agents. Optimal treatment of type 2 diabetes in children, as well as in adults, should go beyond merely achieving euglycemia. Preserving beta cell function in children with impaired glucose tolerance or type 2 diabetes is of critical importance. Thus, clinical trials are needed to establish appropriate and effective treatment regimens for children with type 2 diabetes.

Research Goals and Scope

This RFA solicited investigator-initiated clinical trial proposals for the primary prevention and treatment of children (6 to 18 years of age) with type 2 diabetes. Primary prevention trials will focus on cost-effective, school or community based interventions with the potential for broad, population-wide application. Treatment trials may include lifestyle changes and/or pharmacologic therapy. A desirable goal of a treatment trial will be the assessment of beta cell function (i.e., insulin secretion), as well as glucose control.

Based on peer review, awards will be made to those centers whose proposals are judged to be of high scientific merit. A Steering Committee will then be created, comprised of the Principal Investigator of each study site, the head of the Coordinating Center, as well as an NIDDK representative. The Steering Committee will meet during the planning phase of the cooperative agreement to design the actual study protocols. It is anticipated that the Steering Committee will develop one, multi-arm trial for the treatment of type 2 diabetes in children to be carried out at multiple sites, to insure an adequate sample size, as well as geographic and racial/ethnic diversity. At least one, but possibly more, primary prevention protocols will be developed. The prevention trial ultimately designed by the Steering Committee may involve a standard protocol with variations based on the need for cultural sensitivity at different sites, or the Steering Committee may opt for several distinct prevention trials. If multiple prevention trials at different sites are carried out, the Steering Committee will establish standardized entry criteria, clinical assessments and outcome measures so that all the trials can be compared.

1020 FUNCTIONAL ATLAS OF ORPHAN NUCLEAR RECEPTORS (RFA DK-01-026)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-026.html

FY 2002 Action

This RFA was issued in FY 2001 for FY 2002 funding. Nuclear hormone receptors, their ligands and relevant accessory proteins can serve as the basis for the development of therapeutics to treat disease. Orphan receptors have emerged as important mediators of lipid and carbohydrate metabolism, development, and organogenesis. Understanding the tissue specificity of action will require development of a unique program to elucidate effects on different cells/tissues, role(s) in disease, and differential action in response to ligand(s).

Background

Nuclear receptors comprise a large family of hormone-dependent and -independent transcription factors responsible for reproduction, growth, differentiation, and homeostasis. The nuclear receptor superfamily consists of receptors for steroid hormones (estrogen, androgen, adrenal glucocorticoid and mineralocorticoid, and progesterone; ER, AR, GR, MR, and PR, respectively), nuclear hormones (vitamin D, retinoids, thyroid hormone; VDR, RAR/RXR, TR, respectively), and orphan receptors (peroxisome proliferator activated receptor or PPAR, bile acid receptor, COUP-TFI/II, SF-1, etc.). The latter have functions in cells, during development and in the adult, but with no, or only poorly, defined ligand(s).

Although primarily functioning as transcription factors, it has become clear that the biology of these receptors is complex: they are often bound to chaperone proteins in the cytoplasm, and/or to DNA in the nucleus; they may bind to DNA as monomers, dimers, or heterodimers-with or without ligand; they may interact with any of a number of different classes of nuclear accessory proteins; the presence or absence of ligand can define interactions with other, accessory, proteins, which foster the ability of the receptor to activate or repress gene expression; and alterations in the receptor, the ligand, or various of the accessory proteins, such as co-activators and co-repressors, can have profound effects on development, protein/lipid/carbohydrate metabolism, and in diseases such as prostate and breast cancer, diabetes, obesity, heart disease, and osteoporosis. The receptor, the ligand and relevant accessory proteins can also serve as the basis for the development of therapeutics to treat disease. To do so further research is required to fully understand the molecular mechanism of action of these hormones, the underlying basis for tissue specificity of action, and the nature of cellular co-activator or co-repressor usage and the role(s) these components may play in the development and treatment of disease.

With this in mind, it has become clear that the vast amount of information already available, coupled with the new information emerging from model organisms and from the human genome project, calls for a large-scale, collaborative effort designed to develop, categorize and integrate knowledge of the nuclear receptor superfamily.

Research Goals and Scope

Two overriding objectives govern this initiative: (1) collation and characterization of information already in hand; and (2) new research to more fully understand the role(s) of

orphan nuclear receptors in health, disease, and aging. In developing a Functional Atlas of Orphan Nuclear Receptors, the long-term goal is to focus on orphan receptors (e.g. PPAR, FXR, LXR, SXR, SF-1, CAR, COUP TFI/II, etc.), as well as the cofactors and the ligands with which many interact to complete a functional loop. Among these cofactors are those present in the nuclear compartment (coactivators, corepressors, chromatin modifying proteins and RNA transcripts, linkers, methylases, histone modifying enzymes, etc.), as well as those in the cytoplasmic compartment (chaperones, binding proteins, kinases/phosphatases). Beyond the scope of this present initiative, but certainly relevant in functional contexts, is consideration of the nuclear (VDR, RAR, RXR, TR), and steroid (ER, AR, GR, MR, PR) receptors, as they intersect with ONRs.

Insights into the structures of several receptors both bound and unbound to ligand and/or cofactor(s) have been revealed by x-ray crystallographic and NMR studies. Discovery of natural and artificial ligands has added much to our understanding of function. For some Orphan Nuclear Receptors, role(s) in disease has preceded knowledge of putative ligand(s), as for PPARγ and its role in adipogenesis and insulin resistance in type 2 diabetes mellitus. Indeed, based on less than complete knowledge, several ligands directed at PPARγ have already been developed for use as insulin sensitizing agents in the treatment of type 2 diabetes (e.g. thiazoladinediones; TZDs). The general concept of Selective Receptor Modulators (SRMs) has evolved rapidly to include clinical use of drugs with selective actions on nuclear receptor function, such as TZDs for type 2 diabetes and tamoxifen for estrogen-dependent breast cancer. With greater knowledge of nuclear receptor structure, tissue specificity, and function, in general, it will be possible to develop more powerful and effective SRMs, many of which will be relevant to ONRs.

1029 ISLET/BETA CELL TRANSPLANT REGISTRY (RFP DK-00-005)

http://grants.nih.gov/grants/guide/notice-files/NOT-DK-00-005.html

FY 2002 Action

The objective of this project is to establish a North American islet/beta cell transplant registry that will collect and analyze data both pre- and post-transplantation from all institutions performing these transplants within North America. To be included in this registry will be patient demographics, patient and graft survival rates by area, surgical technique, type of immunosuppression, immunoisolation and/or tolerance induction protocol, donor source, tissue typing, assessment of viral and bacterial contamination in donor tissue, length of graft preservation, implantation site, islet/beta cell preparation procedure and islet/beta cell storage procedure. Metabolic data will also be collected and analyzed. In addition, the data and the results of analyses will be communicated to the scientific community.

Background

In 1989, the NIDDK began funding The International Pancreas Transplant Registry (IPTR), which was established in 1980 by Dr. David Sutherland, University of Minnesota. As part of the IPTR, Dr. Sutherland had entered into a collaborative arrangement with Dr. Konrad Federlin, from the University of Giessen in Germany. Dr. Federlin had instituted an International Islet Cell Transplant Registry. He has focused his efforts on the collection of islet transplant data from throughout the world using forms similar to those of the International Pancreas Transplant Registry. Dr. Sutherland has furnished Dr. Federlin with all the islet transplant data in the IPTR and continues to provide him with prospective information. In exchange, Dr. Federlin furnishes Dr. Sutherland with updates on his islet transplant registry.

In April 1999, an Advisory Committee to the Division of Diabetes, Endocrinology and Metabolic Diseases, NIDDK, recommended the establishment of an Islet/Beta Cell Transplant Registry. With the significant expansion of islet/beta cell transplantation within the U.S., it was recommended that the results of islet/beta cell transplants in the U.S. be collected in a registry independent of the IPTR. This would enable the collection of considerably more information on these transplants.

Research Goals and Scope

This initiative encompasses the establishment of the Islet/Beta Cell Transplant Registry and the provision of statistical, clinical coordination, technical, regulatory, and administrative support for the Registry to collect information on islet or beta cell transplants in patients within North America. This registry will serve as a research tool for the medical community. It is envisioned that this contract will address fundamental questions pertinent to the improvement of host and graft survivals following islet/beta cell transplantation. The contract will also provide support for an independent Data Safety and Monitoring Board that can be used for studies of islet transplantation by investigators in the U.S.

1033 TRANSLATIONAL RESEARCH FOR THE PREVENTION AND CONTROL OF DIABETES (PA-01-069)

http://grants.nih.gov/grants/guide/pa-files/PA-01-069.html

FY 2002 Action

This Program Announcement (PA) solicits research in the translation of recent advances in the prevention and treatment of type 1 or type 2 diabetes into clinical practice for individuals and communities at risk. This PA establishes a diabetes prevention and control program, and seeks applications for clinical and behavioral studies to develop and test strategies for: (1) achieving objectives that have already been proven beneficial, such as control of glycemia and other risk factors for diabetic complications; or (2) enhancing behaviors that are expected to improve health outcomes for individuals with type 1 or type 2 diabetes. Of particular interest are interventions that focus on translating new advances into practice in underserved and minority populations.

Background

The Diabetes Control and Complications Trial (DCCT), for type 1 diabetes, and the United Kingdom Prospective Diabetes Study (UKPDS), for type 2 diabetes, established the importance of intensified diabetes control in dramatically reducing the devastating complications that result from poorly controlled diabetes. Both the DCCT and the UKPDS demonstrated the efficacy of intensified glucose control in reducing the risk for the microvascular complications of diabetes, such as retinopathy, neuropathy, and nephropathy. In addition, results from the UKPDS suggested that strokes may be reduced in patients with type 2 diabetes through a combined regimen of intensive blood pressure and glycemic control. Unfortunately, the advances of these studies have not been successfully incorporated into general health care practice. This underutilization of current knowledge was highlighted in a recent study of diabetic individuals that demonstrated a low frequency of self-monitoring of blood glucose, good glycemic control, regular foot care, and ophthalmic examinations, all of which markedly reduce the incidence and progression of diabetic complications. Alarmingly, less than 2 percent of adults with diabetes receive the level of care that has been recommended by the American Diabetes Association (ADA), with self-monitoring of blood glucose following the ADA guidelines performed by only one in five adults with diabetes. Thus, it is clear that effective mechanisms for diabetes treatment, shown by the DCCT and the UKPDS to reduce the burden of diabetes, are not being implemented.

Ongoing clinical trials are underway that address the prevention of type 1 or type 2 diabetes (e.g., DPT-1 and DPP). The DPP has concluded its randomized intervention phase early, and the results demonstrate that both lifestyle and pharmacologic treatments can significanantly reduce the onset of type 2 diabetes in a high risk population. This important finding will make it even more crucial that effective translation strategies be developed and adopted to improve adherence to accepted standards of diabetes care, and to overcome barriers to the translation of scientific advances into clinical practice.

Research Goals and Scope

This PA solicits applications furthering research in diabetes translation research. Trials proposed under this program should test: (1) improved methods of health care delivery to patients with or at risk of diabetes; (2) improved methods of diabetes self-management; and (3) cost effective community-based strategies to promote healthy lifestyles that will

reduce the risk of diabetes and obesity. Generally, these studies will take interventions that have been demonstrated to be beneficial by controlled laboratory or clinical investigations (e.g., intensive glycemic control), and extend or adapt these interventions to larger populations or other settings. Alternatively, trials may focus on enhancing behaviors (e.g., increased physical activity in individuals at risk for diabetes) generally accepted as likely to improve health outcomes for patients with or at risk of diabetes.

1039 CHROMIUM AS ADJUVANT THERPAY FOR TYPE 2 DIABETES AND IMPAIRED GLUCOSE TOLERANCE (PA-01-114)

http://grants.nih.gov/grants/guide/pa-files/PA-01-114.html

FY 2002 Action

A Program Announcement has been issued, in conjunction with the Office of Dietary Supplements and the National Center for Complementary and Alternative Medicine, to encourage basic and clinical research on the effect of chromium on insulin action and glucose homeostasis. The first applications in response to this PA will be funded in FY 2002.

Background

In vitro studies have suggested that chromium may enhance insulin sensitivity, although its mechanism of action is poorly understood. Several small clinical studies have reported improved glycemic control in patients with diabetes; however, these studies have, for the most part, not been well controlled. Little is known about the chromium status of patients with diabetes, in part because validated measures of whole body chromium have not been established. In addition, further information regarding bioavailability and toxicity is needed for oral chromium preparations. Despite the huge gaps in knowledge, the low cost of chromium makes further research into its potential efficacy as a therapeutic agent in diabetes very attractive. In addition, despite a clear scientific rationale, chromium supplementation is frequently used by the U.S. public for the treatment of diabetes. This widespread use warrants testing of its efficacy and monitoring of its safety for long-term use.

Research Goals and Scope

The purpose of this program announcement is to solicit: (1) basic studies of chromium action on insulin secretory and signaling pathways; and (2) clinical studies to assess the safety and efficacy of chromium as an adjunctive treatment of type 2 diabetes and/or impaired glucose tolerance.

Appropriate topics for investigation under this PA include: (1) small focused phase I and phase II clinical trials to determine the safe and effective dose and formulation of chromium supplementation in individuals with type 2 diabetes or impaired glucose tolerance; (2) studies to establish clinically relevant biomarkers for assessing the efficacy of chromium supplementation in individuals with type 2 diabetes or impaired glucose tolerance; (3) studies to determine factors that predict response to chromium supplementation in individuals with type 2 diabetes or impaired glucose tolerance (e.g., diet, degree of insulin resistance or secretion, duration of diabetes); (4) studies to develop improved techniques for chromium measurement in biological fluids; (5) studies to determine factors that impact on chromium bioavailability; (6) studies to develop tests or biomarkers that can be used to measure and monitor chromium status; (7) studies to develop tests or biomarkers of chromium toxicity, both systemically and at the tissue level; and (8) studies to elucidate the mechanisms by which chromium enhances insulin secretion or action.

1040 THE ROLE OF ANTIOXIDANTS IN THE PREVENTION OF DIABETIC COMPLICATIONS (PA-01-112)
http://grants.nih.gov/grants/guide/pa-files/PA-01-112.html

FY 2002 Action
This Program Announcement has been issued to solicit basic and clinical research applications to study the use of vitamin E and other antioxidants in the prevention or amelioration of diabetic complications. Collaborators include the National Eye Institute (NEI), the National Heart, Lung and Blood Institute (NHLBI), the National Institute on Aging, the National Institute of Neurological Disorders and Stroke, and the NIH Office of Dietary Supplements. The first applications in response to this PA will be funded in FY 2002.

Background
Prevention and treatment of long-term micro- and macrovascular complications remain critical problems in the management of type 1 or type 2 diabetes mellitus. In the U.S., diabetes is the leading cause of new blindness in working-age adults, of new cases of end-stage renal disease and of non-traumatic lower leg amputations. In addition, cardiovascular complications are now the leading cause of diabetes-related morbidity and mortality, particularly among women and the elderly. In adult patients with diabetes, the risk of cardiovascular disease (CVD) is two- to four-fold greater than in the general population.

A growing body of *in vitro* and *in vivo* research indicates that hyperglycemia is associated with increased oxidative stress and endothelial dysfunction. In addition, numerous studies have suggested that patients with diabetes appear to have decreased antioxidant defense capability, measured as lower levels of specific antioxidants, such as ascorbic acid or vitamin E, or reduced activities of antioxidant enzymes, such as catalase, superoxide dismutase or glutathione peroxidase.

In diabetic animals, many, but not all, studies support the use of antioxidant supplementation in reducing various parameters of oxidative stress and in slowing or preventing the development of microvascular complications. Studies in humans have also been promising. Recently, particular interest has focused on the use of vitamin E for the prevention of microvascular complications. Several studies of vitamin E supplementation in diabetic individuals have demonstrated a decrease in biochemical markers of oxidative stress. One small, short-term study of vitamin E supplementation in patients with diabetes showed improvement in some surrogate markers for retinopathy and nephropathy.

A limiting feature of the published studies is that the preparation and dose of vitamin E used has been widely variable. In addition, little data is available regarding potential toxicity of high doses of vitamin E, nor is there data on potential interactions of vitamin E with other nutrients or other antioxidants. Furthermore, interest in mounting a large clinical trial to study the efficacy of vitamin E in preventing diabetic vascular disease has been tempered by the recent negative results of several large, randomized, prospective trials of vitamin E in the prevention of cardiovascular disease and cancer. The negative outcomes of randomized, controlled, prospective trials stand in sharp contrast to the wealth of epidemiologic data suggesting that increased antioxidant consumption is

associated with protection from a variety of diseases. The reason for the discrepancy is not clear.

Given the enormous public health cost of diabetes, the prospect of being able to use a relatively low-cost vitamin supplement to lower the risk of diabetic complications merits further study. The NIDDK, the NIH Office of Dietary Supplements, the NHLBI, the NEI, the National Cancer Institute, and the Juvenile Diabetes Research Foundation International sponsored a workshop on Vitamin E and Diabetic Complications in October 2000. Participants highlighted a number of critical gaps in knowledge, which merit further investigation. This Program Announcement seeks to address some of these important issues.

Research Goals and Scope

This Program Announcement solicits basic or clinical applications to: (1) determine the efficacy and safety of vitamin E or other antioxidants in preventing, delaying or ameliorating the micro- or macrovascular complications of diabetes; and (2) provide insight into the mechanism(s) by which antioxidants might prevent or influence the development of diabetic vascular disease. Epidemiologic or descriptive studies which assess diet or nutritional supplementation, or which simply measure blood levels of oxidants/antioxidants in patients with diabetes will not be considered responsive to this solicitation.

Relevant topics could include: (1) preclinical studies to determine the mechanism(s) by which antioxidant(s) prevent the development of diabetic vascular disease; (2) studies to define interactions between oxidative pathways and free radical formation and the signaling pathways by which insulin, glucose and other factors affect the endothelium; (3) studies to investigate genetic factors that may affect susceptibility to oxidative damage and response to antioxidant therapies in people with diabetes; (4) phase II studies to assess metabolism and tissue distribution, determine kinetics, and establish optimal dosing regimens; (5) studies to establish valid surrogate markers or clinical endpoints of diabetic complications that could be used in phase III trials; (6) studies to determine clinically meaningful, state-of-the-art measures of oxidant/antioxidant status; (7) small trials to compare antioxidants to establish which is most likely to be efficacious in diabetic complications, or to define specific subpopulations who are most likely to benefit from antioxidant intervention; and (8) studies to develop new strategies to inhibit oxidation/glycoxidation and examine the effect of these strategies on microvascular or cardiovascular disease.

1041 DIABETES-FOCUSED SCIENCE EDUCATION IN TRIBAL MIDDLE AND HIGH SCHOOLS (RFA DK-01-033)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-033.html

FY 2002 Action

It is the overall objective of this trans-NIDDK initiative to support faculty at Tribal Colleges and Universities (TCUs) to develop science education programs working with tribal community middle and high schools. It is the intention of this initiative to increase the presence of American Indians in the biomedical sciences by exposing and motivating American Indian students to biomedical science through the prism of diabetes.

Background

The 33 existing TCUs are fully engaged in serving and strengthening local communities. They routinely provide assistance to Indian communities on various programs and projects and are deeply integrated into tribal culture and institutional life. The colleges serve as culturally supportive role models for future success in communities of historically low levels of educational attainment. An association between Tribal Colleges and local schools already exists through the Tribal College Rural Systemic Initiative. This program is part of the Rural Systemic Initiatives in Science, Mathematics and Technology Education Program funded by the National Science Foundation and designed to promote excellence in the teaching of the sciences. The Diabetes-Focused Science Education in Tribal Middle and High Schools program would utilize these existing collaborations to design, test and implement a biomedical science education program around diabetes. The outcome would be increased awareness of diabetes and its risk factors and the role of science in the attainment of health and a healthy lifestyle in a population overburdened with diabetes and its devastating health outcomes. This awareness would be used as the motivational focus for students selecting their future career paths.

Research Goals and Scope

This trans-NIDDK initiative aims to increase the interest and competitiveness of American Indian students in pursuit of biomedical careers.

1042 EXPANSION OF DIABETES RESEARCH CENTERS (RFA DK-01-001, RFA DK-02-004 and RFA DK-02-005)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-001.html

FY 2002 Action

This initiative solicits Diabetes Research and Training Center (DRTC) and Diabetes Endocrinology Research Center (DERC) applications for FY 2002 funding. DERCs and DRTCs support research on diabetes mellitus and its complications, and related areas of endocrinology and metabolism. It is anticipated that support for DERCs and DRTCs will increase in FY 2002 due to increases in the direct cost budgets that can be requested for these centers. If a sufficient number of applications of high merit are received, the number of DERCs may also increase.

Background

The NIDDK currently supports six DRTCs and eight DERCs; all six DRTCs and five DERCs must compete for continued funding in 2002 together with new applications received in response to these solicitations. DRTCs and DERCs are part of an integrated program of support provided by the NIDDK for research in diabetes and related areas of endocrinology and metabolism. Development of new methods to prevent, treat or cure diabetes and its complications will depend on multidisciplinary collaborations among clinical and basic scientists. DRTCs and DERCs provide a focus for enhancing such collaborations among investigators at institutions with an established, comprehensive, federally supported diabetes research base. DRTCs and DERCs are intended to improve the quality and multidisciplinary nature of diabetes research by providing shared access to specialized technical resources and expertise. The overall goal of the DRTC or DERC is to bring together clinical and basic science investigators from relevant disciplines in a manner that will enhance and extend the effectiveness of research related to diabetes and its complications.

Both DERCs and DRTCs require a substantial base of basic and clinical research. In addition DRTCs must have a substantial base of translation of research advances into clinical practice. This includes the identification of barriers to widespread adoption of new science and the development and testing of interventions to overcome these barriers under real world conditions. Applicants are encouraged to focus on underserved populations disproportionately affected by diabetes and pilot and feasibility projects directed at prevention and control of diabetes.

Research Goals and Scope

Diabetes research involves many specialized technologies and other resources, which must be integrated into a cohesive research program. The objectives of the DRTC and DERC are to make these technologies and resources available to many investigators and to promote a multifaceted approach to diabetes research by providing shared resources to investigators with a wide variety of expertise. These centers are based on the core concept. Cores are defined as shared specialized technical resources and/or expertise that enhance efficiency, productivity, multi-disciplinary collaboration, or benefit a group of investigators working in diabetes or diabetes-related areas to accomplish the stated goals of the center.

The DRTCs and DERCs also support a pilot and feasibility program. The pilot and feasibility program provides modest support for new diabetes initiatives or feasibility studies. This program is directed at new investigators or established investigators in other research disciplines whose expertise may be applied to diabetes research. Established diabetes investigators exploring a new research direction related to diabetes are also eligible, but the great majority of pilot and feasibility project support should be directed at new investigators or investigators new to diabetes research.

DRTCs may also include limited funds for an enrichment program to facilitate the exchange of information between investigators who have research interests in the areas of diabetes, endocrinology and metabolism. The enrichment program can support activities such as seminars, guest speakers, visiting scientists, consultants, and workshops.

1043 CYSTIC FIBROSIS SPECIALIZED CENTER OF RESEARCH (SCOR) EXPANSION (RFA DK-01-028)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-028.html

FY 2002 Action

Additional funds are requested in FY 2002 to allow for full funding of a competing CF SCOR. NIDDK issued an RFA to fund a single CF SCOR in FY 2002. The funds available for that competition was below the $750,000 direct cost cap for Center funding so additional funds were allocated to allow the successful applicant to be fully funded if warranted. This should promote increased competition for this Center.

Background

NIDDK currently funds three CF SCORs. SCORs support broadly-based multi-disciplinary or multifaceted research programs pursuing a range of scientific questions with a central research focus. Each SCOR must have a clearly defined, unifying central theme to which each project relates and to which each investigator contributes. This theme must address the central questions relevant to elucidation of the pathogenesis of CF and/or development of new therapeutic approaches for CF. Collectively, these projects should demonstrate essential elements of unity and interdependence and result in a greater contribution to program goals than would occur if each project were pursued individually. These centers provide support for research projects, pilot and feasibility studies, as well as common resources and facilities (cores) that are available to the individual projects comprising the program. In order to be considered for funding, an application must have a minimum of three meritorious research projects. Each core must provide essential functions, services, techniques, determinations or instrumentation that will enhance at least two approved individual research projects.

Research Goals and Scope

Cystic fibrosis is a genetic disease affecting approximately 30,000 persons in the U.S. This disease, which is present from birth, has had improved survival due to better management of the infections and nutritional aspects of the disorder. With the identification of the genetic cause of CF as mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), many studies have been undertaken to identify the functions of this protein and to determine the pathophysiology of the disease. It is clear that CFTR interacts with many other proteins including accessory proteins, scaffolding proteins and other ion channels to carry out its cellular function. Based on our current understanding of the functions and interactions of CFTR, new therapeutic interventions are being evaluated for both their efficacy and their safety. The interactions of researchers from many different backgrounds will be required to translate our understanding of the complex actions of CFTR into therapies for cystic fibrosis.

A multidisciplinary approach to a research objective, which constitutes the central feature of the SCOR, is key to maintaining the rapid expansion of our knowledge of CF. The dramatic progress in understanding the molecular basis of CF has been due in large part to collaborations among scientists with expertise in physiology, cell biology, molecular biology, structural biology, genetics, biochemistry, microbiology, and immunology. Fostering this collaborative effort should accelerate our understanding of the disease and approaches for its treatment.

1047 TREATMENT OF HAART-ASSOCIATED METABOLIC CHANGES IN PATIENTS WITH HIV INFECTION (RFA DK-02-006)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-02-006.html

FY 2002 Action

An RFA will be issued in collaboration with the National Heart, Lung and Blood Institute to encourage applications to develop and test strategies for treating the metabolic complications associated with anti-retroviral drug therapy in patients with HIV infection.

Background

In recent years, the advent of highly active anti-retroviral therapy (HAART) has dramatically improved the survival of patients with HIV infection. Despite the clear benefits of the new anti-retroviral therapies, HAART has been associated with a variety of metabolic complications—including dyslipidemia, insulin resistance and abnormal distribution of body fat (lipodystrophy). These metabolic abnormalities represent major risk factors for the development of other serious diseases, such as diabetes and cardiovascular disease. Even more recently, reports of clinically significant osteopenia have been emerging in HAART-treated patients.

Lipodystrophy, characterized by increased deposition of fat (lipohypertophy) in the abdomen and trunk, and/or loss of fat (lipoatrophy) in the face and extremities, appears to occur commonly in patients on HAART. Currently, it is not clear whether abdominal lipohypertophy is simply accompanied by peripheral lipoatrophy, or whether these changes constitute two separate entities. The lipodystrophic changes have been a particular issue for many affected individuals. In addition to concerns over potential long-term health implications of these body composition changes, distress over these often disfiguring changes has caused some patients to stop taking anti-viral medications.

HAART has also been increasingly associated with hyperinsulinemia and impaired glucose tolerance; to date, frank diabetes has been reportedly less frequently. However, concern about eventual progression to diabetes is real, particularly in those patients who also have accumulation of abdominal (particularly visceral) fat.

Patients receiving HAART frequently develop hypertriglyceridemia, which can be extreme, as well as hypercholesterolemia. Elevated total and LDL-cholesterol levels, which occur following the institution of HAART, may be superimposed on low HDL-cholesterol levels, which have been described in HIV-infected patients prior to initiating any therapy. In non-HIV-infected individuals, co-existence of dyslipidemia and insulin resistance/diabetes confers additive risk for the development of atherosclerotic heart disease, making these HAART-associated side effects a serious potential public health concern.

Large epidemiologic studies are currently ongoing to better describe the metabolic changes associated with HAART and understand whether particular drugs, or classes of drugs, are the etiologic agent(s) of these changes. In addition, a large research effort is aimed at understanding the molecular mechanism(s) by which anti-retroviral drugs might lead to these metabolic abnormalities. A long-term goal of such research might be the development of new, highly-active anti-HIV drugs that lack these adverse metabolic consequences.

In the meantime, it is essential to develop strategies to normalize lipid levels, insulin sensitivity and body fat distribution, and to minimize bone loss in order to enhance patient compliance and decrease the risk for future disease. The safety and efficacy of lipid lowering drugs or diabetes medications have not been extensively studied in patients infected with HIV and/or receiving HAART. It is not known whether adverse drug interactions might affect efficacy and safety, or whether the underlying infection with HIV (or other opportunistic infections), might affect treatment success. For example, the metabolism and clearance of some statins may be affected by concomitant use of protease inhibitors. Some available drugs (e.g., metformin, thiazolidinediones) will be contraindicated because of co-existing renal or liver disease in patients with AIDS. In addition, attention must be paid to other risk factors for diabetes and cardiovascular disease, such as smoking, physical inactivity, diet and hypertension.

Research Goals and Scope

This RFA solicits clinical studies to: (1) test the efficacy, in patients infected with HIV, of agents currently approved for the treatment of dyslipidemia, insulin resistance or diabetes, and osteoporosis/osteopenia; and (2) develop and test novel treatment approaches to the metabolic consequences of anti-HIV therapy, including lipodystrophy.

Appropriate topics for investigation under this RFA would include: (1) studies to examine the effects of currently available pharmacotherapies for the treatment of insulin resistance or diabetes, hypercholesterolemia and/or hypertriglyceridemia, and osteoporosis or osteopenia in the metabolic syndromes associated with HAART; (2) studies to identify potential drug interactions between HAART and current pharmacotherapies for the treatment of insulin resistance or diabetes, hypercholesterolemia and/or hypertriglyceridemia, and osteoporosis or osteopenia; (3) studies to identify and test new therapies to prevent or reverse the metabolic complications associated with HAART; (4) studies to evaluate the efficacy of diet and exercise alone, or in combination with medication, in reversing dyslipidemia and insulin resistance/diabetes in patients on HAART; (5) studies to evaluate whether switching anti-HIV drugs is an effective approach to the treatment of metabolic changes; and (6) studies to test agents that affect fat deposition and/or metabolism for the treatment of HAART-associated lipodystrophy.

1062 GENE THERAPY FOR NEUROLOGICAL DISORDERS (RFA NS-02-007)
http://grants.nih.gov/grants/guide/rfa-files/RFA-NS-02-007.html

FY 2002 Action
The NIDDK has joined the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Child Health and Human Development, the National Institute on Aging, and the National Institute on Deafness and Other Communications Disorders to issue an RFA for Gene Therapy for Neurological Disorders. This RFA is intended to encourage research projects that address translational issues in the context of specific neurological disorders.

Background
Gene transfer methodologies may ultimately be used to treat a broad spectrum of diseases that affect the nervous system. These include neurodegenerative disorders, stroke, epilepsy, and many genetic diseases such as lysosomal storage disorders. The brain presents unique challenges to achieving successful gene transfer. Because the brain contains many distinct cell types and is regionally heterogeneous, determining how to deliver therapeutic genes effectively is critical. The presence of the blood-brain barrier, limited access to the brain, and the post-mitotic state of brain cells make introducing genes and ensuring that they are correctly expressed difficult.

Recent studies indicate that, despite these problems, gene transfer has great potential as a therapeutic modality. Using modified viral vectors, liposomes, genetically-modified cells, or direct DNA transfer, researchers have delivered a variety of therapeutic genes into animal models. Many of these pre-clinical experiments have been extremely successful. For example, in a recent NINDS-sponsored workshop (Gene Therapy for Neurological Disorders, October 23-24, 2000), investigators described the successful treatment of animal models of Parkinson's disease and of specific lysosomal storage disorders, which is summarized in *Molecular Therapy* **3**:3-7, 2001.

Research Goals and Scope
Projects submitted in response to this RFA should focus on specific scientific, technological, or safety issues that must be addressed prior to the initiation of clinical trials. Possible scientific/technological goals include: (1) the development of improved inducible vectors that permit effective temporal control over transgene expression; (2) the design of vectors with regulatory elements that permit gene expression to be targeted to specific brain regions, peripheral neural tissues, or to other cell types of therapeutic interest; (3) the development of methods that achieve higher transduction efficiencies and high-level, stable transgene expression in the nervous system; (4) the development of techniques that permit improved focal or global delivery of vectors into the brain or peripheral neural tissues; (5) the development of improved methods for monitoring transgene expression in the brain; (6) toxicology studies and the determination of optimal dosage regimens for specific vector/transgene constructs; (7) the investigation of the long-term effects of expression of specific therapeutic transgenes; (8) the development of viral vectors that overcome problems of toxicity and immune response; and (9) the use of large animal models to address safety issues.

DIVISION OF DIABETES, ENDOCRINOLOGY AND METABOLIC DISEASES
Conferences and Workshops

Pancreatic Development, Proliferation and Stem Cells
(Co-sponsored by the American Diabetes Association and Juvenile Diabetes Research Foundation International)
October 18-19, 2001
http://www.niddk.nih.gov/health/pancreatic/stem/index.htm
Replacement or regeneration of beta cells damaged in diabetes are therapeutic interventions that hold promise in the future treatment of diabetes. However, the development of such therapies will be enhanced with a fundamental understanding of the developmental biology underlying formation of the endocrine pancreas, of the mechanisms regulating beta cell mass, and of stem cells. The objective of this two-day workshop is to bring together investigators from multiple disciplines doing state-of-the-art research in developmental biology of the pancreas, islet cell biology and stem cells.

Etiology and Epidemiology of Early Autoimmune Type 1 Diabetes in Humans
(Co-sponsored by the American Diabetes Association, the Centers for Disease Control and Prevention, the Juvenile Diabetes Research Foundation International, the National Institute of Allergy and Infectious Diseases, the National Institute of Child Health and Human Development, and the National Institute of Environmental Health Sciences)
October 25-26, 2001
This international conference will explore approaches to identifying environmental triggers of type 1 diabetes. It is anticipated that recommendations will be implemented through a collaborative effort of TrialNet and ITN and through population based studies.

Beta Cell Biology In the 21st Century
(Co-sponsored by the American Diabetes Association, the Juvenile Diabetes Research Foundation International, Lilly Research Labs, and OSI Pharmaceuticals)
November 26-28, 2001
http://www.betacellbiology.niddk.nih.gov/
The development of new treatments for diabetes depends on a thorough understanding of the basic biology of the pancreatic beta cell. Especially important are efforts to understand the signaling networks that operate in the cell. This workshop will showcase recent progress in beta cell biology and exciting new results in other systems that will impact future work in the beta cell.

Encapsulation of Islets
(Co-sponsored by the Juvenile Diabetes Research Foundation International, NASA, and the National Center for Research Resources)
December 2001
This conference will bring together cell biologists, immunologists and bio-engineers to examine new approaches to encapsulation of islets.

Asymptomatic Primary Hyperparathyroidism: A Perspective for the 21st Century
April 8-9, 2002
The workshop will build on the progress made since the 1990 Consensus Development Conference on Primary Hyperparathyroidism and attempt to define the current state-of-the-art in our understanding of the molecular and clinical nature of the disease with the aim of understanding the present status of medical versus surgical management.

2002 MPS Symposium—Challenges in Treating the Brain
(Sponsored by the National Institute of Neurological Disorders and Stroke, co-sponsored by the National Institute of Child Health and Human Development)
September 2002